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**13. ABSTRACT (Maximum 200 Words)**
This project is to explore an innovative CAD strategy for improving early detection of breast cancer in screening mammograms by focusing on computerized analysis and detection of cancers missed by radiologists. The research in the second year is on (i) continuation of missed cancer analysis with a focus on density analysis and its effect on CAD detection; (ii) new CAD system design. The achievements include (1) A comprehensive analysis was taken on the effect of breast density on cancer detection. The accomplishments include breast dense tissue segmentation, correlation analysis of mammogram density features between missed and detected stages, statistical testing of density difference between normal and cancerous mammograms, baseline study of the effect of density on CAD detection performance using existing algorithm. (2) A new CAD system was designed based on the existing secondgeneration
CAD algorithm and the missed cancer analysis. Due to the effective modification strategies taken in the new system, detection performance was improved for mammograms at both detected and missed stages. However, with the focus on missed cancer analysis and detection, a bigger improvement was obtained in detecting missed cases even though the general detection performance is still lower than that at detected stage.

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## INTRODUCTION

This project is to explore an innovative CAD strategy for improving early detection of breast cancer in screening mammograms by focusing on computerized analysis and detection of cancers missed by radiologists. Due to the unpredictable difficulty in data collection, the first year of research was fallen behind the schedule. Considering the fact that there is limit time and budget left and more importantly based on the research we have done so far, two things were done in the past year. First we requested a revision of the Statement of Work to focus on the important research items, which has been approved by DoD. Secondly we tried our best to catch up the schedule. A big progress was made in the second year research.

## BODY

***Objective 1:* to determine the effect of density pattern on cancers detection**

***Accomplishments:***

*(1) Segmentation of glandular regions in mammogram*

An automatic approach was applied in mammographic dense tissue segmentation. It is a statistical-based method developed in our lab [1]. The segmentations were taken on both cancerous and normal mammograms at screening-detected and screening-missed stages respectively. The percentage of segmented density tissue area out of the whole breast area is calculated as the index of breast density. Figure 1 shows the histograms of density index of three different type mammograms. To check the correlation of density between mammograms at missed and detected stages, two kinds of correlation analysis, i.e. Pearson's correlation and Spearman's Rank correlation, were taken [2]. The Pearson correlation coefficient measures the strength and direction of a *linear* relationship between two variables. One problem is that if there are outliers in the data, Pearson's correlation coefficient will be greatly affected. Also, Pearson's correlation coefficient only measures linear relationships between variables. Spearman's rank correlation coefficient is a nonparametric (distribution-free) rank statistic which is a measure of strength of the associations between two variables. As this measure depends only on ranks it is not affected by outliers. The correlation coefficients are listed in Table 1. It is observed that (i) there is a good consistency between the Pearson's correlation and Spearman's Rank correlation, i.e. no significant outliers exist in density segmentation; (ii) the breast density segmented at missed stage is correlated to that at detected stage; (iii) the segmentation correlation between normal mammograms at missed and detected stages is higher than that with cancerous mammograms. An explanation is that the cancerous mammogram usually has more complicated density pattern and is statistically of higher density as shown below, which makes big variations in segmentation.

Table 1. Correlation of Density Segmentation.

| Variable 1 | Variable 2 | Pearson's correlation coefficients | Spearman's correlation coefficients |
|---|---|---|---|
| Missed_cancer | Detected_cancer | 0.5896 | 0.5946 |
| Missed_normal | Detected_normal | 0.6908 | 0.6882 |

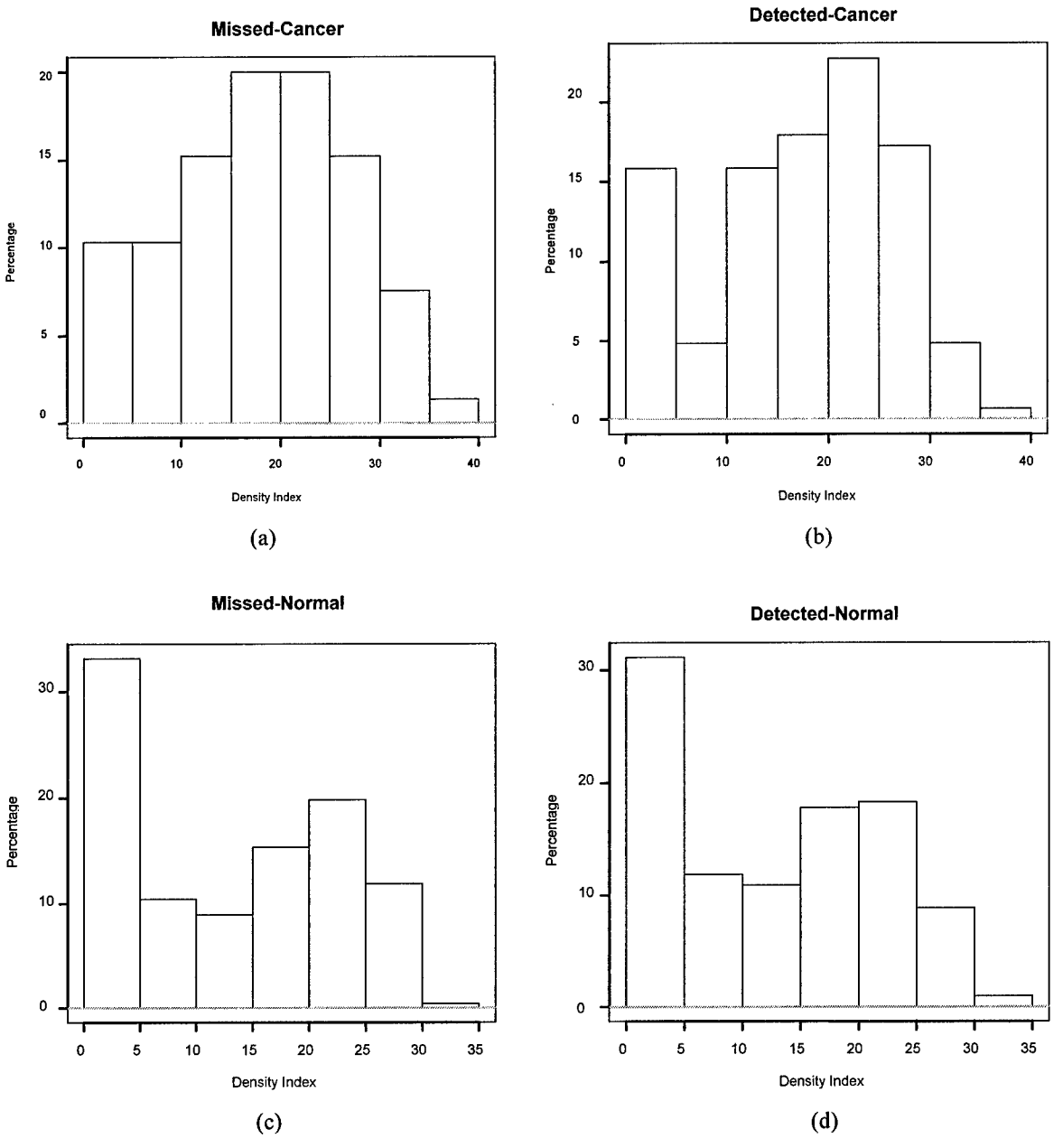



Figure 1. Histograms of breast density: (a) cancerous mammogram at missed stage; (b) cancerous mammogram at detected stage; (c) normal mammogram at missed stage; (d) normal mammogram at detected stage.

*(2) Density analysis of normal and cancerous mammograms*

A set of statistical testing was taken to exam (i) Is there any difference in density between the mammograms at the detected stage and that at missed stage? (ii) Is there any difference in density between the normal mammograms and the cancerous mammograms? Listed in Table 2 are the p-values of T-test and Wilcoxon rank test for density difference between detected stage mammogram and missed stage mammogram, and the normal mammogram and cancerous mammogram respectively. If the difference of density index is normally distributed, we use t-test otherwise use Wilcoxon rank test. If the test $p$-value is less than 0.05, we have evidence to reject null hypothesis that the mean of difference is zero at significant level 0.05, i.e. significantly different [2]. It is observed that (i) there is no significant change in density of mammograms at detected and missed stages for both the normal and cancerous mammograms. It is because most of the mammograms at missed and detected stages were taken in consecutive years as shown in

Figure 2, during which no significant change could have happened on breast. (ii) There is a significant difference in density between normal and cancerous mammograms at both detected and missed stages. Specifically the cancerous mammograms have a higher density than normal mammograms.

Table 2. Statistical Test of Density Difference

| Variable 1 | Variable 2 | T– test p-value | Wilcoxon test p-value |
|---|---|---|---|
| Missed_cancer | Detected_cancer | 0.4793 | 0.5919 |
| Missed_normal | Detected_normal | 0.6708 | 0.5326 |
| Missed_cancer | Missed _normal | 5.977e-07 | 3.339e-06 |
| Detected_cancer | Detected_normal | 2.579e-06 | 5.067e-06 |

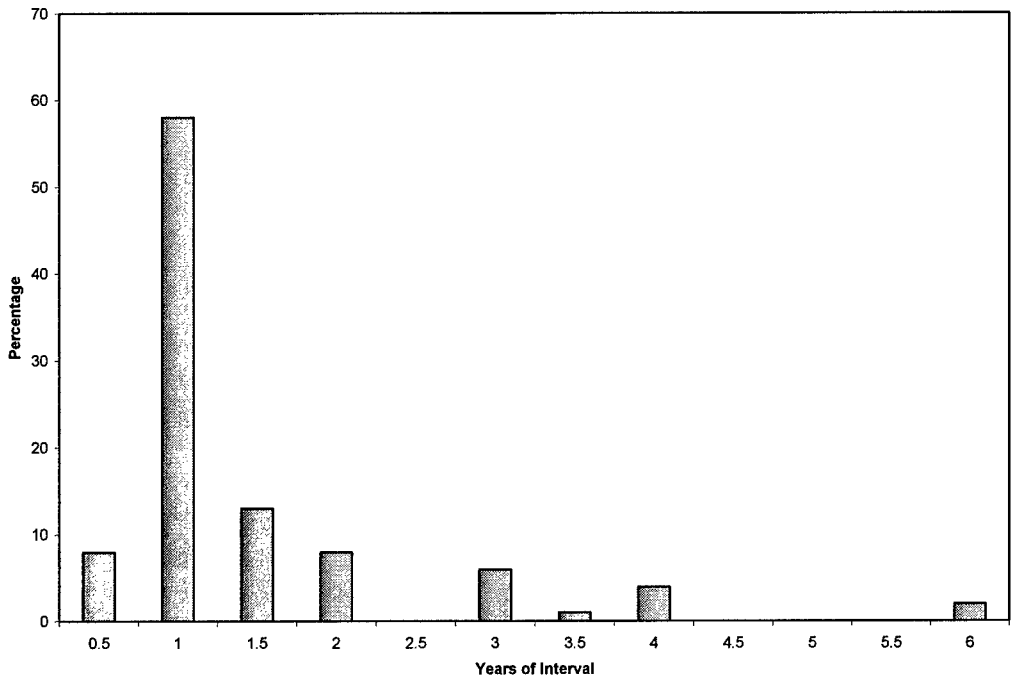



Figure 2. A distribution of interval between mammograms taken at missed and detected stages.

*(3) Effect of density pattern on CAD detection performance*

In the study described above, we have demonstrated the statistical difference in breast density between the normal and cancerous mammograms. It has also been reported that the lesions occurred in dense breasts are statistically more likely to be missed in screening mammogram [3]. However there are few reports on study of the effect of density on CAD detection performance, especially that at different detection stages. In this research, as a baseline study, we used our existing CAD algorithm for detection testing on the serial database with an intention to examine the differences in detection performance for cases with different breast density. The detailed technical information on the CAD algorithm can be found in [4][5].

Wolf applied a method of classification of parenchymal patterns that used qualitative, as well as

quantitative criteria. He described a four category image classification method based on the amounts of density and duct work present, designated by N1, P1, P2, and DY [6]. N1 category refers to parenchyma composed primary of fat with, at most, small amounts of dysplasia; no ducts visible. The P1 corresponds to the presence of prominent duct work that occupies up to one-quarter of breast volume. P2 category refers to sever involvement, with prominent ductal pattern occupying more than one-fourth the volume of breast. DY refers to mostly dense tissue. Due to the limited size of database, in order to obtain a statistically significant result, we classify the mammograms into two categories with density percentages less or more than 25% respectively, which roughly correspond to categories (N1, P1) and (P2, DY) in Wolf's classification. Figure 2 and 3 show the FROC curves of CAD detection results of high (>25%) and low (<25%) density cases at missed and detected stages respectively. *Please note that the sensitivity is defined here as hit rate per image. If the criteria of detection were defined as the lesion is marked by CAD on one or both mammographic views, which is used by most commercial CAD system evaluation reports, we could expect a much higher sensitivity at the same false positive rates (per image).* It is observed that (i) the detection performance on less dense case is better than that on high dense cases. In other words, similar to the radiologists in mammogram screening, the lesions occurred in dense breasts are more likely to be missed in CAD detection; (ii) the difference of detection performance between high and low dense cases is smaller at the detection stage than that at missed stage, i.e. the lesions on dense mammograms are even more difficult to detect compared to the lesions on low dense mammograms at the missed stage.

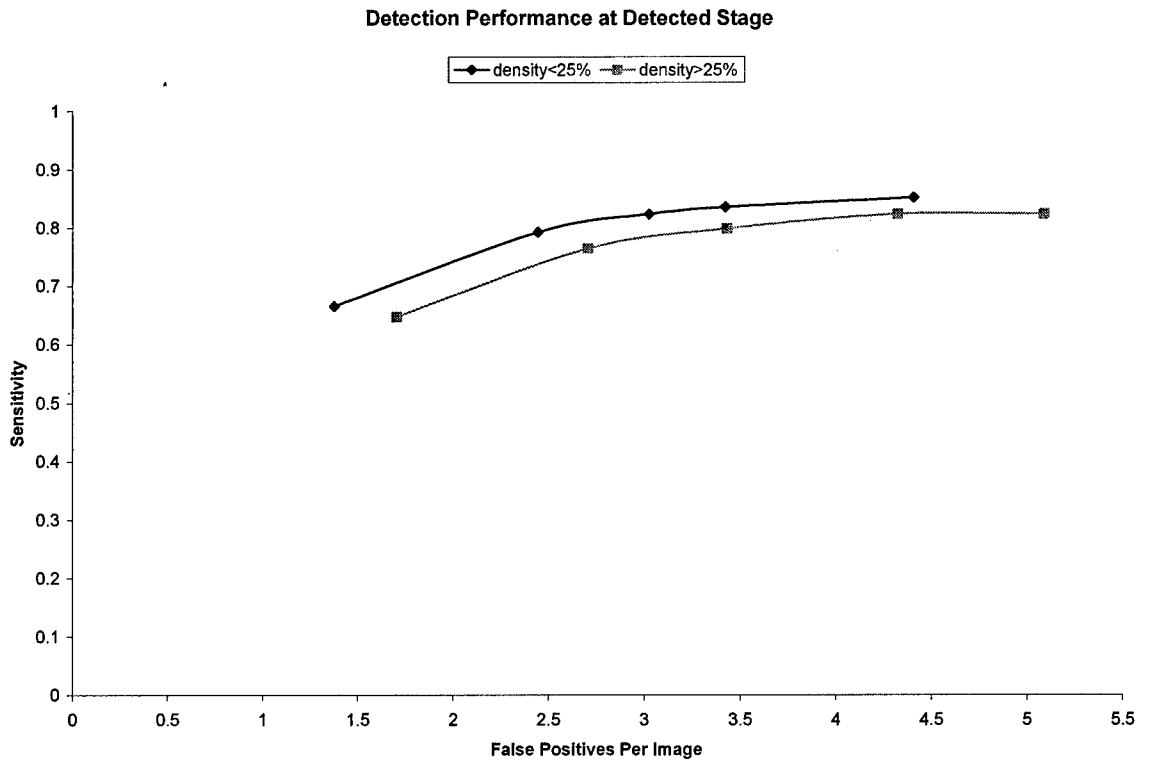



Figure 3. FROC curves of CAD cancer detection on mammograms at screening detected stage.

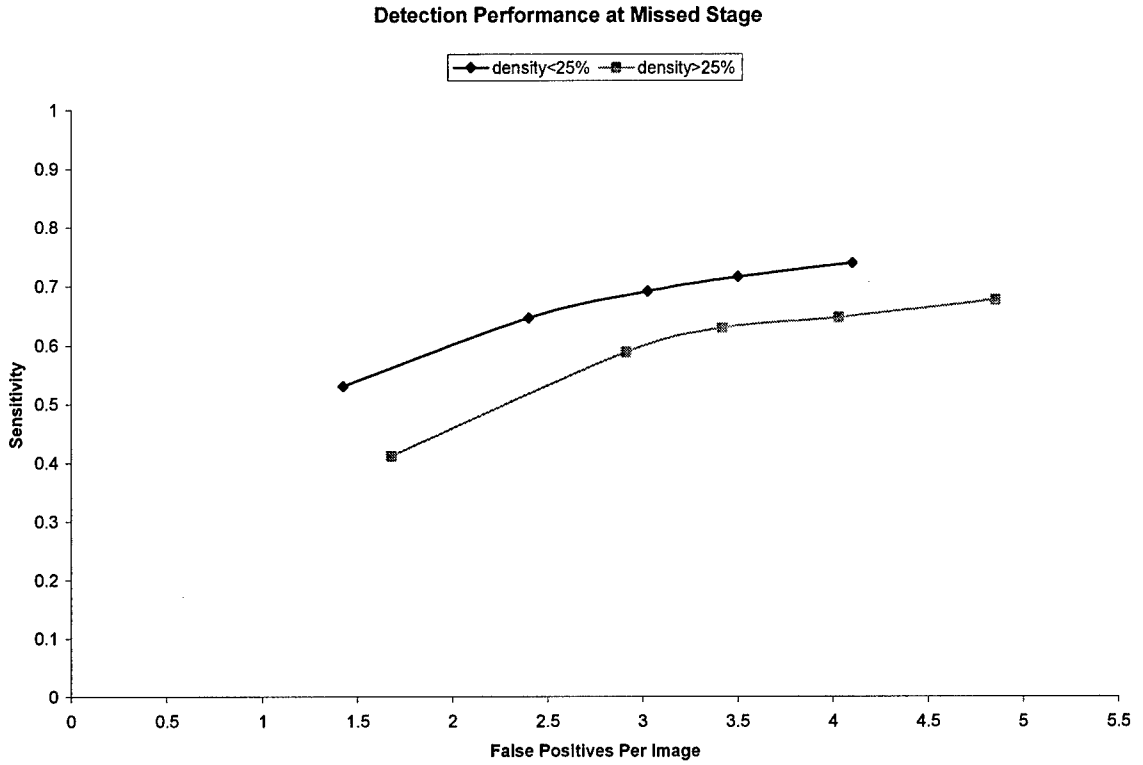


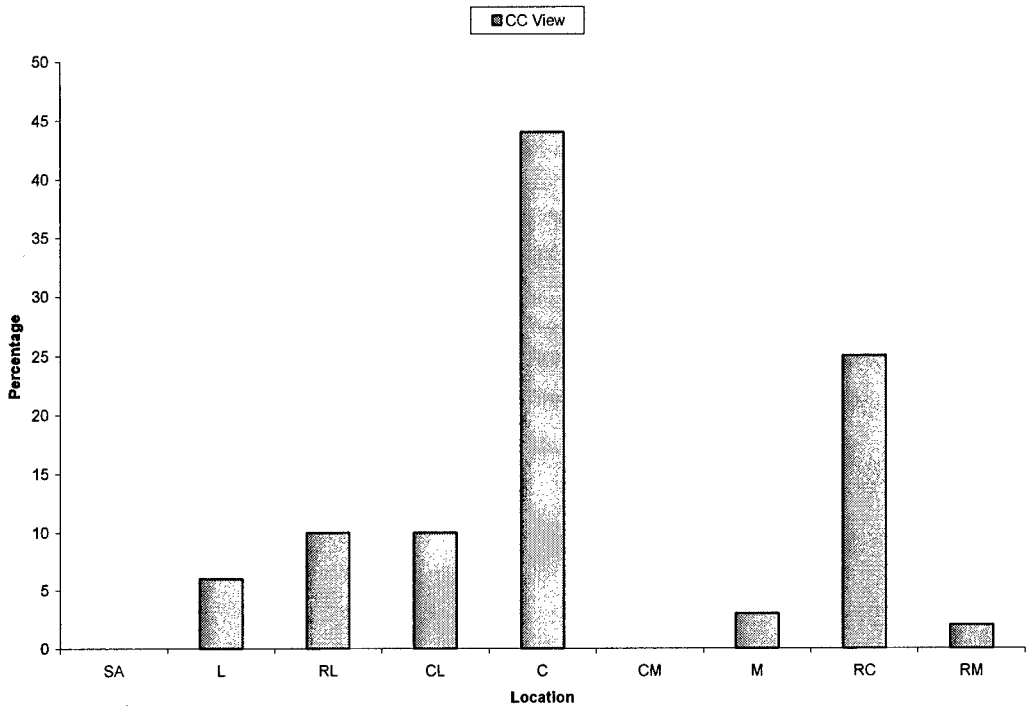

Figure 4. FROC curves of CAD cancer detection on mammograms at screening missed stage.

***Objective 2: to design new CAD system for improving missed cancer detection***

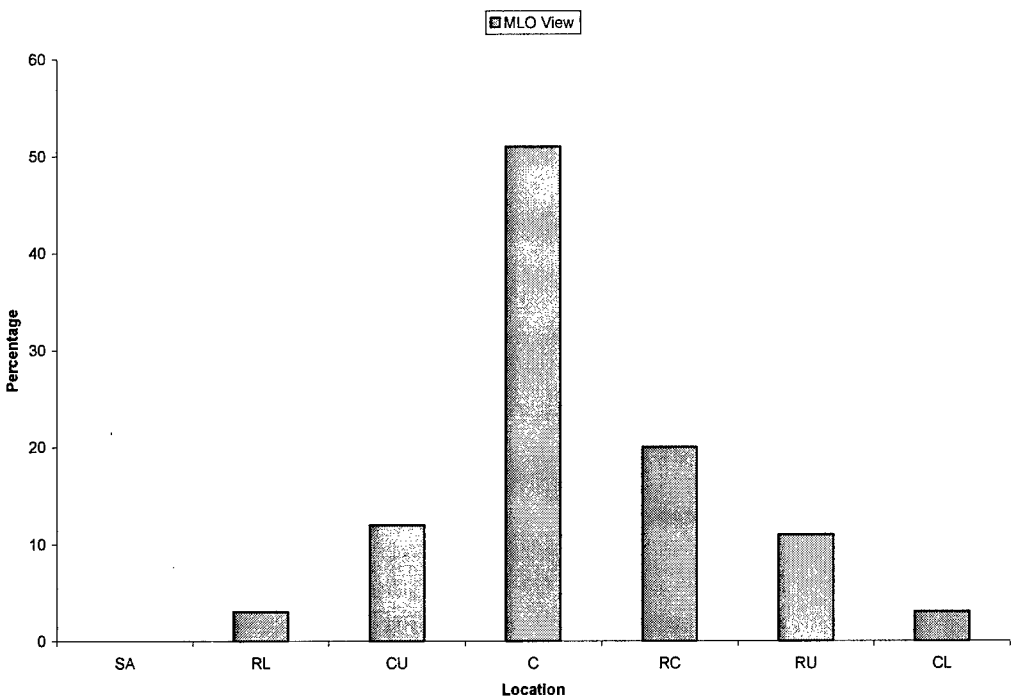
***Accomplishments:***

The new CAD system is based on our two generations of CAD algorithms for mass detection using digitized mammogram [4][5] and incorporates the analysis results of missed cancer in the design. The strategies taken in this study include *(a) Multi-mode detection by breast density classification:* It has been demonstrated in the baseline testing study by using existing CAD algorithm that the lesions occurred in dense breasts are more likely to be missed in CAD detection. Therefore, in order to improve the detection of missed cancer, a multi-mode detection was performed by classifying the mammogram with breast density index as defined above before an appropriate detection mode is applied to the detection. As explained above, due to the limited size of database in this study, each input mammogram was classified into two categories corresponding to density percentages less or more than 25%. *(b) Breast area partition and region based adaptive detection*: Due to the fact that the location of cancer appearance in mammograms has a big variation in missing probability in screening mammogram, breast area partition provides the basis for further adaptive processing. The partition process consists of three steps: (i) breast boundary and nipple detection; (ii) pectoral muscle and view (CC or MLO) identification; (iii) area partition. Figure 5 shows the likelihood of missed cancers in each region. *(c) Weighted classification using the distinguishing features identified in missed cancer analysis*: The classification is a modified hybrid structure in which (i) a combined "hard" and "soft" decision classification strategy was applied [4][5]; (ii) decision thresholds were adjusted based on the missed cancer feature analysis. For example, a significant difference in feature "mass size" was observed between detected and missed stages, therefore the threshold for this feature in decision tree was reduced in order to enhance the chance of missed cancer to be detected; (iii) candidate competition are weighted using region likelihood value. Figure 6 and Figure 7 show the FROC curves of detection on mammograms of missed and detected cancer stages before and

after improvement. It is observed that the new CAD system provides a better detection performance at both missed and detected stages. However, because the new CAD is designed with focus on missed cancer, a bigger improvement is obtained for missed cancer detection.




(a)




(b)

Figure 5. Distribution of cancers at different locations on (a) CC view and (b) MLO view, where SA=Subareol, C=Central, CL=Lower-Central, CU=Upper-Central, RC=Central-Retroglandular, RU=Upper-Retroglandular, RL=Lower-Retroglandular, L=Lateral, CL=Central-Lateral, CM=Medial-Central, RM=Medial-Retroglandular, RL=Lateral-Retroglandular.

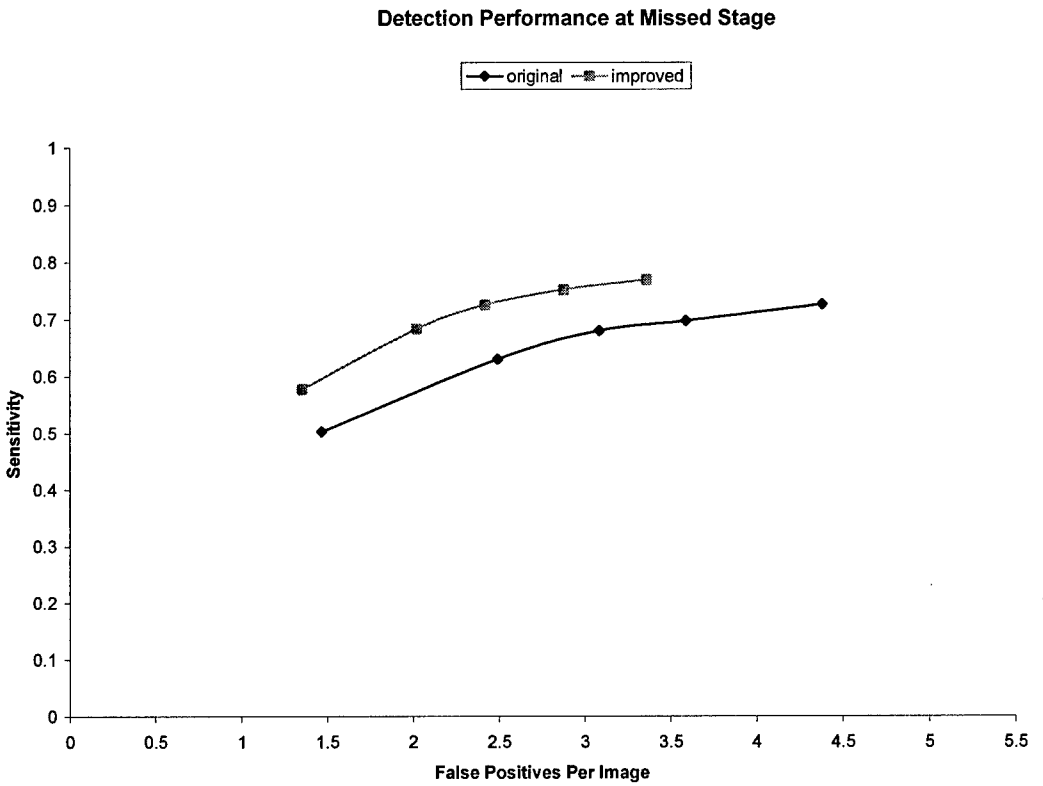



Figure 6. Improvement of CAD cancer detection on mammograms at screening missed stage.

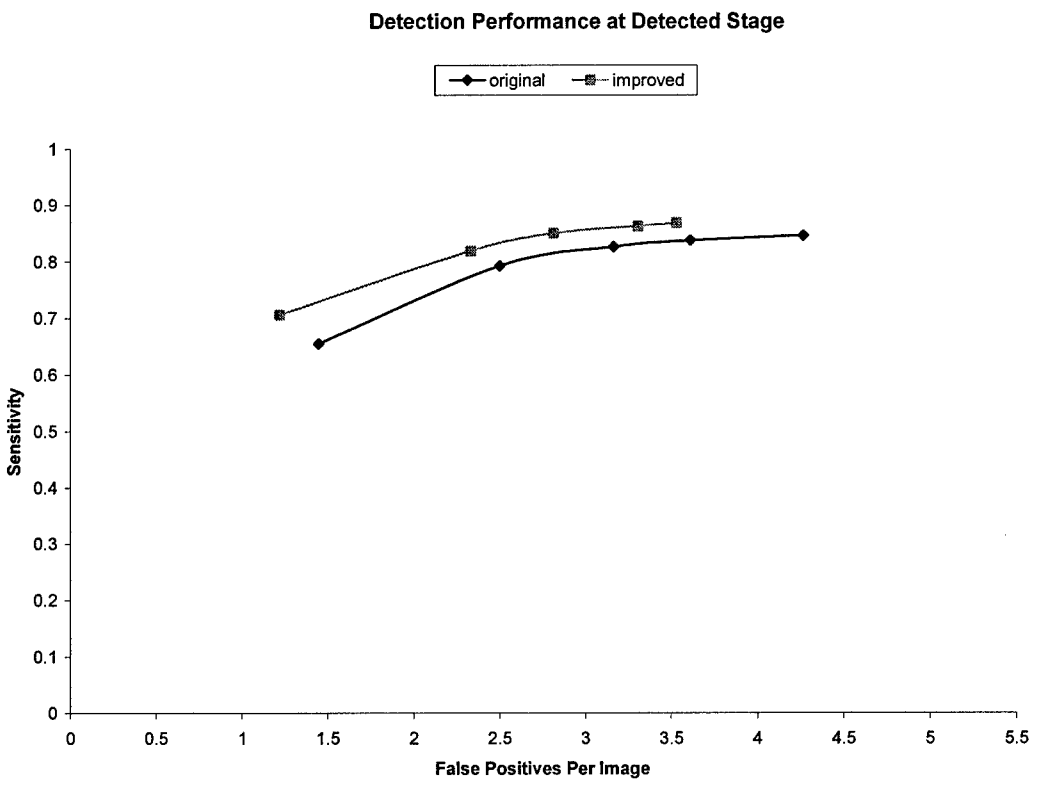



Figure 7. Improvement of CAD cancer detection on mammograms at screening detected stage.

## KEY RESEARCH ACCOMPLISHMENTS

1. A comprehensive analysis was taken on the effect of breast density on cancer detection. The accomplishments include breast dense tissue segmentation, correlation analysis of mammogram density features between missed and detected stages, statistical testing of density difference between normal and cancerous mammograms, baseline study of the effect of density on CAD detection performance using existing algorithm.
2. A new CAD system was designed based on the existing second-generation CAD algorithm and the missed cancer analysis. Due to the effective modification strategies taken in the new system, detection performance was improved for mammograms at both detected and missed stages. However, with the focus on missed cancer analysis and detection, a bigger improvement was obtained in detecting missed cases even though the general detection performance is still lower than that at detected stage.

## REPORTABLE OUTCOMES

*1. Presentation and/or proceedings paper*

(a) Lihua Li, Zuobao Wu, Zhao Chen, Angela Salem, Maria Kallergi, Claudia G. Berman "Statistical Analysis of Missed Cancer Features in Screening Mammography," Proceedings of SPIE Medical Imaging, 2005.

## CONCLUSIONS

This project is to explore an innovative CAD strategy for improving early detection of breast cancer in screening mammograms by focusing on computerized analysis and detection of cancers missed by radiologists. The research in this second year is on (i) continuation of missed cancer analysis with a focus on density analysis and its effect on CAD detection; (ii) new CAD system design. A big progress has been made in this past year. The results demonstrated the effectiveness of this study in improving detection performance.

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